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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,214	12/01/2003	Muraleedharan G. Nair	MSU 4.1-672	4443

21036 7590 12/16/2009

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ART UNIT	PAPER NUMBER
1655	
MAIL DATE	DELIVERY MODE
12/16/2009	PAPER

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MURALEEDHARAN G. NAIR,
YANJUN ZHANG, and SHAIJU K. VAREED

Appeal 2009-005344[1]
Application 10/725,214
Technology Center 1600

Decided: December 16, 2009

Before TONI R. SCHEINER, FRANCISCO C. PRATS, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to methods of suppressing cancer. The Examiner rejected the claims as lacking enablement. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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[1] The Board of Trustees operating Michigan State University, East Lansing, Michigan is the real party in interest.

STATEMENT OF THE CASE

Claims 1 and 5-7 stand rejected and are appealed (App. Br. 2). Those claims read as follows:

> 1. A method for *in vivo* suppression in a mammal of multiplicity in the stomach, colon and in both the stomach and colon of cancer cells which comprises:
>
> providing an effective amount of a composition which consists essentially of malvidin as an active ingredient to the mammal so as to suppress the multiplicity of the cells.
>
> 5. The method of Claim 1 wherein the cells are in a mammal and the malvidin is fed orally to the mammal.
>
> 6. The method of Claim 1 wherein the composition is in a pharmaceutical carrier.
>
> 7. The method of Claim 1 wherein the stomach cell is AGS and the colon cell is HCT 116 both as maintained by the American Type Culture Collection.

The Examiner cites the following documents as evidence of unpatentability:

Christine Gorman, *How to Tell the Hype from the Hope: A Special Report*, TIME, May 18, 1998, at 37.

Trisha Gura, *Cancer Models: Systems for Identifying New Drugs are Often Faulty*, 278 SCIENCE 1041-42 (1997).

Rakesh K. Jain, *Delivery of Molecular Medicine to Solid Tumors*, 271 SCIENCE 1079-1080 (1996).

Katsube et al., *Induction of Apoptosis in Cancer Cells by Bilberry (Vaccinium myrtillus) and the Anthocyanins*, 51 JOURNAL OF AGRICULTURAL AND FOOD SCIENCE 68-75 (2003).

Oshima et al., *Suppression of Intestinal Polyposis in Apc$^{\Delta 716}$ Knockout Mice by Inhibition of Cyclooxygenase 2 (COX-2)*, 87 CELL 803-809 (1996).

Masuko Kobori, *In Vitro-Screening for Cancer-Suppressive Effect of Food Components*, 37 JARQ 159-165 (2003).

Hou et al., *Anthocyanidins inhibit cyclooxgenase-2 expression in LPS-evoked macrophages: Structure-activity relationship and molecular mechanisms involved*, 70 BIOCHEMICAL PHARMACOLOGY 417-425 (2005).

The sole rejection before us for review is the Examiner's rejection of claims 1 and 5-7 under 35 U.S.C. 112, first paragraph, as lacking enablement (*see* Ans. 4-9).

ENABLEMENT

ISSUE

Citing the well known factors set forth in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), the Examiner initially contrasts the breadth of the claims, which encompass using malvidin to suppress the "multiplicity of any and all stomach or colon cancer cells in both the stomach and colon" (Ans. 5), with the Specification's disclosure of only *in vitro* inhibition of cultured colon cancer (HCT-116) cells and stomach cancer (AGS) with the claimed agent (*id.* at 6).

The Examiner notes that "the state of the art at the time of filing of the present specification suggested that the delivery of therapeutic drugs which exhibit anti-tumor activity in cancer models do not necessarily have the same beneficial functional effect in humans" (*id.* at 7 (citing Gorman, Gura, and Jain)). The Examiner further notes that Appellants' disclosure of inhibiting colon cancer cells with malvidin is directly contradicted by Katsube's disclosure that "'[o]nly pure delphindin and the glycoside isolated

from the bilberry extract, but not malvidin and the glycoside, inhibited the growth of HCT 116 cells'" (*id.* at 8 (citing Katsube)).

Thus, the Examiner contends, "[g]iven the insufficient guidance in the specification as to how to carry out the instantly claimed invention, the lack of working examples, the lack of correlative working examples, and the state of the art at the time the specification was filed," practicing the claimed method "would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan" (*id.* at 8-9).

Appellants initially note that "[d]etailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention" (App. Br. 7 (citing MPEP § 2164)). For example, Appellants urge, "[c]ompliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed" (*id.* at 14).

Appellants contend that the "level of one of ordinary skill relating [to] the suppression of a multiplicity of cancer cells in the stomach and/or colon was high at the time the application was filed" (*id.* at 8 (citing Declaration of Muraleedharan Nair under 37 C.F.R. § 1.132 (entered June 29, 2006), Barranco I, and Barranco II)).[2]

Appellants argue that, as evidenced by the Declaration of Muraleedharan Nair entered October 10, 2006, "there is predictability in the

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[2] S.C. Barranco et al., *Heterogeneous responses of an in vitro model of human stomach cancer to anticancer drugs*, 1 INVEST. NEW DRUGS 117-27 (1983) (abstract only ("Barranco I"); S.C. Barranco et al., *Establishment and characterization of an in vitro model system for human adenocarcinoma of the stomach*, 43 CANCER RES. 1703-9 (1983) (abstract only) ("Barranco II").

art of *in vivo* suppression of multiplicity of cancer cells of the stomach and/or colon, where *in vitro* tests have been performed in that show the activity of a cancer treatment against stomach (AGS) or colon (HCT-116) cancer cell lines" (*id.* at 10 (citing Kang)).[3]

Appellants contend that HCT-116 cells are "an *in-vitro* model that is recognized as correlating to the specific condition of colon cancer" and that AGS cells are "an *in-vitro* model that is recognized in the art as correlating to the specific condition of stomach cancer" (*id.* at 11-12 (citing Nair Declaration of June 29, 2006, Gieseg,[4] Barranco I, and Barranco II)).

Thus, Appellants argue, when the art recognizes that a particular *in vitro* model correlates to treating a specific condition, the model "should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition" (*id.* at 12-13 (citing *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995))).

In view of the positions advanced by Appellants and the Examiner, the issue with respect to this rejection is whether Appellants have shown that the Examiner erred in concluding that the Specification's disclosure of using malvidin to inhibit the viability of cultured HCT116 colon cancer cells and AGS stomach cancer cells would not have enabled a skilled artisan to

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[3] Kang et al., *Tart cherry anthocyanins inhibit tumor development in Apc^{Min} mice and reduce proliferation of human colon cancer cells*, 194 CANCER LETTERS 13-19 (2003).

[4] Gieseg et al., *The influence of tumor size and environment on gene expression in commonly used human tumor lines*, 4 BMC CANCER 35 (2004).

practice a method of "*in vivo* suppression in a mammal of multiplicity in the stomach, colon and in both the stomach and colon of cancer cells," as recited in claim 1, without undue experimentation.

FINDINGS OF FACT ("FF")

1. The Specification discloses that the "Min" mouse line is a line of mice "predisposed to multiple intestinal neoplasia (Min) result[ing] from a mutation in the murine homolog of the adenomatous polyposis coli (APC) gene" (Spec. [0006]). According to the Specification, the Min mouse line "has been proposed to be a model for the study of human colorectal cancer" (*id.*).

2. The Specification discloses experiments in which the effects of anthocyanins, cyanidins, and red tart cherries were compared to the effects of control diets, as well as sulindac-containing diets, in Min mice (*see id.* at [0036]-[0042]).

3. The mouse experiments did not evaluate the effects of malvidin by itself (*see id.*).

4. The Specification discloses experiments in which cultures of the HCT-116 colon cell line and the AGS stomach cell line were challenged with different concentrations of a number of compounds including malvidin, and the percentage of viable cells remaining after the challenge was determined (*id.* at [0044]-[0045]). "The experiments were performed in triplicate at concentrations of 25, 50, 100 and 200 μg/mL" of malvidin.

5. The results of the HCT-116 and AGS tests are presented in Figure 7, reproduced below:

FIGURE 7

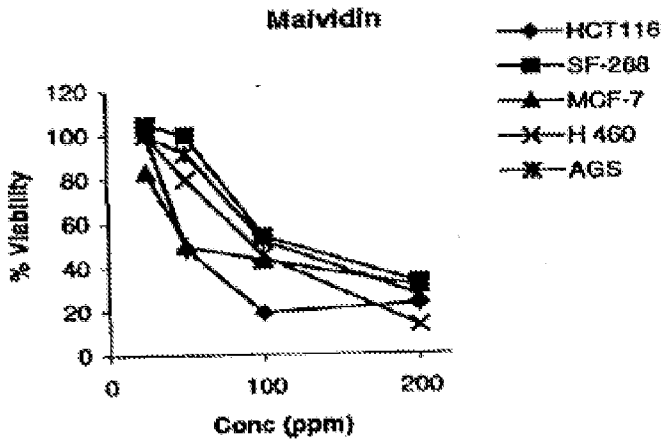

Figure 7 shows a line graph of cell viability versus malvidin concentration in parts per million when treated *in vitro*.

6. Gorman discloses that, despite encouraging results for certain cancer treatments in mice, scientists recognize that "curing a disease in lab animals is not the [same] as doing it in humans" (Gorman 40).

7. Gura discloses that, although screening potential anti-cancer drugs seems like an easy matter of determining whether the compound kills or inhibits the tumor cell of choice, "since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the U.S. Food and Drug Administration" (Gura 1041).

8. Gura reports that "'[t]he fundamental problem in drug discovery for cancer is that the model systems are not predictive at all'" (*id.* (quoting Alan Oliff executive director for cancer research at Merck Research Laboratories)).

9. Gura discloses, for example, that a mutant mouse strain lacking the APC gene, "seems to do well at re-creating the early signs of colon cancer. But in the later stages of the disease, the type of mutations in the tumors begin to diverge from those in human colon cancer, and the disease manifests itself differently as well" (*id.*).

10. Jain discloses that, while antibodies, cytokines, antisense oligonucleotides, gene-targeting vectors, and genetically engineered cells have "potent effect on cancer cells in vitro and in some in vivo tumor systems," and are therefore "heralded as breakthrough drugs . . . clinical results to date have not met the high expectations extrapolated from carefully planned and performed preclinical studies" for a number of reasons (Jain 1079-1080).

11. Katsube "investigated the growth inhibitory effects of 10 edible berry extracts on two different cancer cell lines. Bilberry extract was found to be most effective for inhibiting HL60 human leukemia and HCT116 human colon carcinoma cells in vitro. Bilberry extracts and anthocyanins purified from them induced apoptosis in HL60 cells but little in HCT116 cells" (Katsube 68).

12. Regarding the purified compounds, Katsube specifically discloses that "[o]nly pure delphindin and the glycoside isolated from the bilberry extract, but not malvidin and the glycoside, inhibited the growth of HCT116 cells" (*id.* (Abstract)).

13. Kobori "investigated important anti-cancer effects, that is, growth-inhibitory and apoptosis-inducing effects of some food and food components on cancer cells" (Kobori 159 (abstract)). According to Kobori "[b]ilberry ethanol extract strongly inhibited the growth of HL60 and HCT116 human

colon carcinoma cells, and also induced apoptosis in HL60 cells but not in HCT116 cells" (*id.*).

14. Kobori also discloses that the "anthocyanidins, delphinidin and malvidin, inhibited cell growth and induced apoptosis in HL60 cells. Delphinidin, but not malvidin inhibited the HCT116 cell growth" (*id.*).

15. Oshima investigated "the role of COX-2 [cyclooxygenase 2 enzyme] in colorectal tumorigenesis" (Oshima 803). Oshima was able to significantly reduce the number of polyps in APC knockout mice using a COX-2 inhibitor (*id.*).

16. Based on their experiments, Oshima concludes that it "present[s] the first evidence that COX-2 plays a key role in polyp formation and demonstrate[s] the basis for chemopreventive treatment of polyposis and cancer by inhibitors of COX-2" (*id.* at 808).

17. Hou investigated the "effects of anthocyanidins, the aglycon nucleuses of anthocyanins widely occurring in reddish fruits and vegetables, on the expression of cyclooxygenase-2 (COX-2) . . . in lipopolysaccharide (LPS)-activated murine macrophage RAW264 cells" (Hou 417 (abstract)).

18. Hou discloses that "[o]f five anthocyanidins, delphinidin and cyanidin inhibited LPS-induced COX-2 expression, but pelargonidin, peonidin and malvidin did not" thus suggesting that "the *ortho*-dihydroxyphenyl structure of anthocyanidins on the B-ring appears to be related with the inhibitory actions" (*id*).

19. In the Declaration of Muraleedharan Nair under 37 C.F.R. § 1.132 (entered June 29, 2006), Professor Nair states:

> (7.) That "HCT-116" is an *in-vitro* model that is recognized as correlating to the specific condition of colon cancer as evidenced by the enclosed publication, Gieseg . . . .

> (8.) That "AGS" is an *in-vitro* model that is recognized in the art as correlating to the specific condition of stomach cancer as evidenced by the enclosed abstracts, Barranco [I] and Barranco [II] . . . .

(Nair Declaration 3 (entered June 29, 2006).)

20. Gieseg investigated "whether gene expression changed significantly as a tumor increased in size, we analyzed samples from two human colon carcinoma lines (Colo205 and HCT-116) at three different sizes (200 mg, 500 mg and 1000 mg)" (Gieseg 35). Furthermore, "[t]o investigate whether gene expression was influenced by the strain of mouse, tumor samples isolated from C.B- 17 SCID and Nu/Nu mice were also compared" (*id.*).

21. Barranco I states that "[f]our permanent clones of a human adenocarcinoma of the stomach and the parent line from which they were isolated were used as an in vitro model system to evaluate the effects of 8 anticancer agents on cell survival" (Barranco I, abstract).

22. Barranco I states that "[t]he studies reported here indicate that this human stomach cancer model can provide valuable insight into the design of clinical protocols for treatment of gastric carcinoma in man" (*id.*).

23. Barranco I does not mention the specific cell line used in its experiments.

24. Barranco II states that "[t]en permanent clones derived from a single biopsy specimen of an untreated human adenocarcinoma of the stomach were established and characterized in vitro" (Barranco II, abstract).

25. Barranco II states:

> It is important to characterize human tumor cells in vitro in this detailed manner, since they serve as excellent model systems for other studies involving the heterogeneous responses to

> drugs and radiation. The identification of mechanisms of drug sensitivity and resistance and the testing of drug and radiation combination treatment schedules in such in vitro systems can provide valuable insight into the design of clinical protocols for treatment of stomach cancer in humans.

(*Id.*)

26. Barranco II does not state which specific cell lines were used in its experiments.

27. In the Declaration of Muraleedharan Nair under 37 C.F.R. § 1.132 (entered October 10, 2006), Professor Nair states:

> (1.) That [the Kang article] . . ., of which he is one of the authors, clearly shows that there is a direct correlation between *in vitro* and oral *in vivo* use in suppressing multiplicity of human cancer cells of the stomach or colon with anthocyanins and cyanidin. Malvidin is a related compound to cyanidin (see Figures 1 and 2 of the application). It would be expected by one skilled in the art that there would be a similar correlation with *in vitro* and *in vivo* use of malvidin to suppress multiplicity of stomach or colon cancer cells . . . .
> (2.) That in his opinion, the results with malvidin *in vitro* are predictive of *in vivo* activity suppressing multiplicity of cancer cells based upon his research as set forth in [Kang].

(Nair Declaration 2 (entered October 10, 2006).[5])

28. Kang discloses:

> [W]e conducted experiments to test the potential of anthocyanins to inhibit intestinal tumor development in Apc^{Min} mice and growth of human colon cancer cell lines. Mice consuming the cherry diet, anthocyanins, or cyanidin had significantly fewer and smaller cecal adenomas than mice consuming the control diet or sulindac. Colonic tumor numbers

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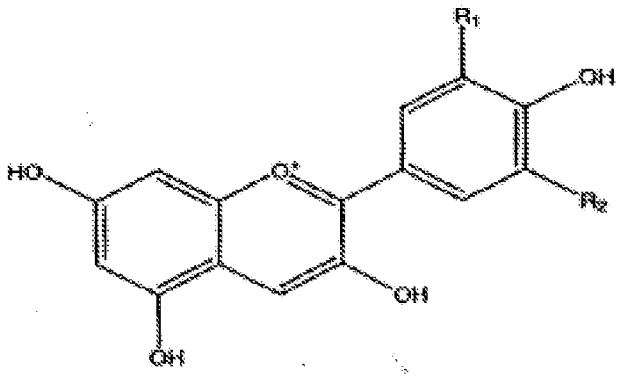
[5] This document is not paginated. We therefore refer to page 1 as the first page, and the other pages as if paginated consecutively.

> and volume were not significantly influenced by treatment. Anthocyanins and cyanidin also reduced cell growth of human colon cancer cell lines HT 29 and HCT 116. The IC_{50} of anthocyanins and cyanidin was 780 and 63 μM for HT 29 cells, respectively and 285 and 85 μM for HCT 116 cells, respectively. These results suggest that tart cherry anthocyanins and cyanidin may reduce the risk of colon cancer.

(Kang 13 (abstract).)

29. Appellants' Figure 2 is reproduced below:



Anthocyanidin	R_1	R_2
Cyanidin	H	OH
Delphinidin	OH	OH
Malvidin	OCH_3	OCH_3
Pelargonidin	H	H
Petunidin	OCH_3	OH

FIGURE 2

The figure shows the structures of five anthocyanidins, including cyanidin and malvidin.

PRINCIPLES OF LAW

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . . After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

Thus, when making an enablement rejection, the Examiner must reasonably explain why "the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement" *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

Once the Examiner meets this burden, however, "the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling." *Id.*

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

In re Wands, 858 F.2d at 736-37 (citations omitted).

Moreover, "[working] examples are not required to satisfy section 112, first paragraph." *In re Strahilevitz*, 668 F.2d 1229, 1232 (CCPA 1982). For example, in *Falko-Gunter Falkner v. Inglis*, the court affirmed this

Board's conclusion that claims to a modified pox virus vaccine were enabled, despite the fact that the specification focused on viruses other than pox virus, provided no examples directed to pox virus, and discussed pox virus only in general terms relating to the inventive disclosure. *Falko-Gunter Falkner v. Inglis,* 448 F.3d 1357, 1365 (Fed. Cir. 2006).

Thus, as noted in *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334 (Fed. Cir. 2003):

> The enablement requirement is often more indulgent than the written description requirement. The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation."

ANALYSIS

Appellants' arguments do not persuade us that the Examiner erred in concluding that the Specification does not enable the full scope of the subject matter encompassed by claim 1. Rather, a preponderance of the evidence supports the Examiner's contention that an ordinary artisan would have expected that practicing the full scope of the claimed method would require undue experimentation.

The Examiner does not appear to dispute that the level of skill in this art is high, and we agree with Appellants that, when this is the case, the disclosure need not be overly detailed. Moreover, as Appellants urge, the Specification discloses that the claimed therapeutic agent, malvidin, has *in vitro* activity against both a stomach cancer cell line, AGS, and a colon cancer cell line, HCT-116 (FF 4-5).

The Examiner has, however, provided specific evidence which, in our view, would have caused a skilled artisan to doubt whether Appellants' *in vitro* data would translate, in a predictable fashion, to the *in vivo* treatment methods encompassed by claim 1. As the Examiner points out, Hou discloses that malvidin does not inhibit the *in vitro* expression of COX-2 (FF 17-18), an enzyme shown by Oshima as playing "a key role in polyp formation and [which] demonstrate[s] the basis for chemopreventive treatment of polyposis and cancer by inhibitors of COX-2" (FF 16).

Moreover, both Katsube and Kobori disclose that malvidin does not inhibit HCT-116 cells *in vitro* (FF 11-14). Thus, using the same cell line, and the same therapeutic agent, prior art practitioners obtained results entirely different than Appellants.

In view of the inconsistent results obtained in HCT-116 cells in the hands of different practitioners, we are not persuaded that a skilled artisan following the Specification's teachings would have expected to be able to treat a multiplicity of colon tumors *in vivo* without undue experimentation. Despite Appellants' showing that malvidin can act to inhibit HCT-116 cells in certain circumstances, the overall inconsistent results obtained when challenging HCT-116 cells with malvidin *in vitro*, as demonstrated by the prior art cited by the Examiner, suggests that practicing the *in vivo* methods encompassed by claim 1 would have required more than routine experimentation.

We acknowledge Gieseg's use of HCT-116 cells in tumor studies, discussed in the first Nair Declaration (FF 19, 20). However, the inconsistent results with respect to malvidin and HCT-116 cells, discussed

above, suggest that HCT-116 cells are not an adequate colon cancer model, at least with respect to malvidin.

Moreover, if the HCT-116 cells are considered to be predictive of *in vivo* effectiveness of cancer agents, as Appellants posit, the negative results obtained by Katsube and Kobori would have suggested that malvidin was not suitable as a colon cancer-treating agent. This further bolsters the Examiner's position that determining how to use malvidin in treating colon cancer would have required a degree of experimentation that a skilled artisan would have considered undue.

We also acknowledge, as pointed out in the first Nair Declaration, the disclosures in the Barranco abstracts of using stomach cancer cell lines *in vitro* to test the effectiveness of anti-cancer agents (FF 19, 21-25). However, the first Nair Declaration does not positively state that Barranco actually uses or discusses AGS cells. Rather, the Declaration simply says that the Barranco abstracts are "evidence[]" that AGS cells are a correlative model (FF 19). The Barranco abstracts, in turn, do not specifically state that "AGS" cells are the cells lines that were evaluated and discussed.

Thus, on the current record, it is not clear whether the statements in the Barranco abstracts are directed to AGS cells. More importantly, however, claim 1 is not limited to treating tumors in the stomach, but also encompasses treating colon tumors. As discussed above, the Examiner has provided specific evidence casting doubt on whether the *in vitro* model used in the Specification adequately enables the *in vivo* methods encompassed by claim 1.

We further acknowledge Kang's disclosure that cyanidin, a compound similar to malvidin (*see* FF 29), inhibited cultured HCT-116 cells, and also

resulted in fewer and smaller cecal tumors in a mouse model when compared to a control diet, though "[c]olonic tumor numbers and volume were not significantly influenced by treatment" (FF 28). Overall, however, Kang states that its "results suggest that tart cherry anthocyanins and cyanidin may reduce the risk of colon cancer" (*id.*).

We further acknowledge the statement in the second Nair Declaration that, based on the Kang reference, it "would be expected by one skilled in the art that there would be a similar correlation with *in vitro* and *in vivo* use of malvidin to suppress multiplicity of stomach or colon cancer cells" (FF 27).

We are not persuaded, however, that this evidence demonstrates error in the Examiner's prima facie case of non-enablement. It might be true that a compound similar to malvidin had success in both an *in vitro* and an animal model.

However, as discussed above, the Examiner has proffered direct evidence showing that the claimed compound at issue, rather than merely a similar one, lacks *in vitro* activity in the very same colon cancer line urged by Appellants as being predictive of *in vivo* effectiveness. Because the evidence advanced by the Examiner is directed to the claimed compound, rather than merely a similar one, we consider it much more probative than Kang of whether an ordinary artisan would consider the claim, and its supporting disclosure, enabling.

In sum, Appellants' arguments do not persuade us that the Examiner erred in concluding that the Specification's disclosure of using malvidin to inhibit the viability of cultured HCT116 colon cancer cells and AGS stomach cancer cells would have enabled a skilled artisan to practice a

method of "*in vivo* suppression in a mammal of multiplicity in the stomach, colon and in both the stomach and colon of cancer cells," as recited in claim 1, without undue experimentation.

We accordingly affirm the Examiner's enablement rejection of claim 1, as well as claims 5-7, which were not argued separately. *See* 37 C.F.R. § 41.37(c)(1)(vii).

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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